REMARKS

Claims 1-25 were pending in this application. Claims 1, 3, 5-8, 12, 14, 16, 17, 20, and 22-25 have been amended. Claims 9, 10, 18 and 19 have been cancelled without prejudice. Claims 26 and 27 have been added. No new matter is introduced by these amendments. Support for the claim amendments and new claims is discussed below, where necessary.

After entry of this amendment **claims 1-8, 11-17, and 20-27 are pending in this application**. Consideration of the pending claims is requested.

Preliminary Amendment:

Applicants thank the Examiner for entering the Preliminary Amendment, filed December 5, 2001, with this U.S. National Stage application filing.

Information Disclosure Statement ("IDS"):

Applicants thank the Examiner for considering the IDS, filed December 5, 2001, with this U.S. National Stage application filing, and for returning a copy of the Form 1449 initialed by the Examiner.

***Claim Rejections under 35 U.S.C. §112, 1st paragraph*:**

Claims 12-21 and 25 have been rejected under 35 U.S.C. §112, 1st paragraph because the specification allegedly does not provide enablement for detecting the presence of *Treponema pallidum* in a biological sample. Applicants traverse this rejection on the grounds that one of skill in the art would recognize that indirect detection of anti-lipoidal antibodies in a sample is a well known and long-standing measure of the presence of *T. pallidum* in the sample. However, to further prosecution of this application, independent claims 12 and 25 (and therefore dependent claims 2-21) have been amended, in relevant part, to recite methods of detecting anti-lipoidal antibodies.

The Office action (at page 2, paragraph 5) states that the specification is "enabling for a method of detecting anti-lipoidal antibodies." Thus, in view of the amendments to claim 12 and 25 and the Office action finding, Applicants request that the rejection be withdrawn.

Claim 16 has been rejected under 35 U.S.C. §112, 1st paragraph because the specification allegedly does not provide enablement for the concentration of cardiolipin of approximately between 0.01 and 0.05% in the claimed composition. Applicants traverse this rejection and request reconsideration.

The Office action (page 4, paragraph 6) cites four of the *In re Wands* factors (*i.e.*, quantity of experimentation necessary, the amount of guidance presented, the nature of the invention and the predictability in the art), and contends that Applicants have "not provided adequate guidance" for "the quantity of experimentation needed" and that "there is a great deal of unpredictability in specificity and sensitivity of serological detection of syphilis." In support of this contention, the Office action merely states that the specification (i) "fails to provide a specific methodological procedure for which the instant method can or is intended to be used," and (ii) "fails to mention any specific significance of the [percentage] cardiolipin in the composition."

The Patent Office bears the burden of establishing a *prima facie* case of non-enablement (MPEP §2164.04). MPEP §2164.01(a) directs that "[i]t is improper to conclude that a disclosure is not enabling based on an analysis of only one of the [*Wands*] factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole." Furthermore, a recitation of the *Wand* factors alone is insufficient to support an enablement rejection, and reasons and evidence must also be provided (MPEP §2164.04).

The present enablement rejection is supported by a mere recitation of some of the *Wands* factors and, arguably, by two reasons related only to one of such factors (*i.e.*, the amount of guidance provided by the specification). Thus, the burden for establishing nonenablement has not been met, and the rejection should be withdrawn.

Moreover, the claimed range of cardiolipin concentrations, *i.e.*, 0.01 to 0.05%, is enabled by claim 16 itself. MPEP §2164 expressly recognizes that claim limitations "may enable one

skilled in the art to make and use the claim containing the limitation." Thus, original claim 16 teaches the synthetic cardiolipin concentration of 0.01 to 0.05% by volume. The specification clearly teaches one of skill in the art how to (i) prepare the synthetic cardiolipin-containing composition useful in the claimed method (see, *e.g.*, page 12, line 30 through page 13, line 7), and (ii) carry out the claimed method (see, *e.g.*, page 13, line 10 through page 16, line 15).

The Office action recognizes (at page 4, paragraph 6) that the specification enables the method of claim 16 comprising synthetic cardiolipin in the range of 0.02 to 0.04% by volume. It is only a small step requiring no undue experimentation for one of skill in the art to perform routine experiments to make and use in the claimed method a composition comprising, for example, 0.01% synthetic cardiolipin by volume as compared to 0.02%, or comprising, for example, 0.05% synthetic cardiolipin by volume as compared to 0.04%.

On the basis of the foregoing arguments, Applicants request that this rejection be withdrawn.

***Claim Rejections under 35 U.S.C. §112, 2nd paragraph*:**

Claims 2-8, 11, 13-14, 16-17, and 22-25 have been rejected under 35 U.S.C. §112, 2nd paragraph because the terms "approximately" and "between approximately" in claims 3, 5-8, 14, 16-17 and 22-25 are relative terms that allegedly render the claims indefinite. Applicants traverse this rejection on the grounds that those of skill in the art would understand the term "approximately" when used in the context of the claimed values. However, to further prosecution of the application, claims 3, 5-8, 14, 16, 17, and 22-25 have been amended to substitute the term "about" for the term "approximately." The Federal Circuit holds that the term "about" is not indefinite under 35 U.S.C. §112, ¶2 (see, *e.g.*, BJ Service Company v. Halliburton Energy Services, 2003 U.S. App. LEXIS 16074, Fed. Cir., decided August 6, 2003; a copy of which is attached as Exhibit A).

Claims 2, 4, 11, and 13 do not contain the allegedly indefinite term, and the Office action provides no further specific basis for rejection of these claims.

On the basis of these arguments and amendments, Applicants request that this rejection be withdrawn.

***Claim Rejections under 35 U.S.C. §102*:**

Claims 1-8, 11, and 22 have been rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Yabusaki, U.S. Pat. No. 4,738,932, issued April 19, 1988 ("Yabusaki"). Applicants traverse this rejection on the grounds that one of skill in the art would understand that isolated, natural cardiolipin and lecithin are not "synthetic substances."

Claim 1 has been amended to recite "[a]n antigen composition comprising tetramyristoyl cardiolipin and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine." Yabusaki teaches natural cardiolipin isolated from beef heart (see, *e.g.*, column 3, line 10). Yabusaki does not describe, either expressly or inherently, the forms of synthetic cardiolipin and synthetic lecithin recited in amended claim 1. Claims 2-8, 11 and 22 each depend from amended claim 1. Thus, Yabusaki cannot anticipate claim 1 as amended and its dependent claims. Applicants request that the rejection be withdrawn.

Claims 1-8, 11, and 22 have been rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Barner and Boguth, U.S. Pat. No. 4,307,074, issued December 22, 1981 ("Barner").

As discussed above, claim 1 has been amended to recite, in relevant part, "tetramyristoyl cardiolipin and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine." Barner does not describe, either expressly or inherently, either of these compounds. Thus, Barner cannot anticipate claim 1 as amended and its dependent claims 2-8, 11 and 22. Applicants request that the rejection be withdrawn.

Claims 1-2, 4, and 9 have been rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Gokhale *et al.*, *British Journal of Cancer*, 74(1):43-48, 1996 ("Gokhale").

As discussed above, claim 1 has been amended to recite, in relevant part, "1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine." Gokhale does not describe, either expressly or inherently, this synthetic lecithin compound. Moreover, Gokhale does not describe an "antigen" as recited in claim 1. Rather, Gokhale describes the formation of liposomes for use in drug delivery. For both of the foregoing reasons, Gokhale cannot anticipate amended claim 1 or its dependent claims 2 and 4. Claim 9 has been cancelled. Thus, Applicants request that this rejection be withdrawn.

Claims 12-17, and 20-21 have been rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Yabusaki.

Claim 12 has been amended to recite, in relevant part, "a composition comprising tetramyristoyl cardiolipin and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine . . ." Yabusaki does not describe, either expressly or inherently, the forms of synthetic cardiolipin and synthetic lecithin recited in amended claim 12. Claims 13-17, 20 and 21 each depend from amended claim 12. Thus, Yabusaki cannot anticipate claim 12, as amended, or its dependent claims. Applicants request that this rejection be withdrawn.

Claims 12-17, and 20-21 have been rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Barner.

As discussed above, claim 12 has been amended to recite, in relevant part, "a composition comprising tetramyristoyl cardiolipin and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine . . ." Barner does not describe, either expressly or inherently, either of these compounds. Thus, Barner cannot anticipate amended claim 12 or its dependent claims 13-17, 20, and 21. Applicants request that the rejection be withdrawn.

Claim Rejections under 35 U.S.C. §103:

Claims 1, 9, 10, and 22-24 have been rejected under 35 U.S.C. §103 as allegedly being unpatentable over Yabusaki in view of Avanti Polar Lipids product numbers 710332 (1,1',2,2'-tetramyristoyl cardiolipin) and 850457 (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine). Applicants traverse this rejection on the grounds that a *prima facie* case of obviousness has not been established.

As an initial matter, claims 9 and 10 have been cancelled; therefore, the rejection is moot with regard to those claims.

With regard to claims 1 and 22-24, the Office action contends (at page 11, paragraph 16) that one of skill in the art would have made use of the synthetic cardiolipin and synthetic lecithin, which were commercially available from Avanti Polar Lipids, to obtain the claimed compositions. To the contrary, without the teaching of Applicants' specification, one of skill in the art would not have any reason to combine tetramyristoyl cardiolipin and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine at all (see, amended claim 1), much less combine such compounds in the concentrations recited in amended claims 22-24. Moreover, prior to Applicants' disclosure, there was no expectation of success even if the combination was made.

Naturally occurring cardiolipin contains four fatty acid side chains, and naturally occurring lecithin contains two fatty acid side chains. Even in nature, the fatty acid side chains of both cardiolipin and lecithin can have considerable variability, for example, in terms of length of chain, and/or in terms of asymmetry or symmetry (*i.e.*, whether the fatty acid side chains on the same molecule have the same or different chemical structures), and/or in terms of degree of saturation (*i.e.*, whether fully saturated or having various degrees of unsaturation). Thus, even the naturally occurring forms of these compounds can be numerous and variable. This possible structural variability is compounded by synthetic cardiolipins and lecithins where it is possible to *independently* modify the length of, and/or degree of saturation in *each* of the fatty acid side chains, and add substitutions, if desired. For example, a single manufacturer alone (*i.e.*, Avanti Polar Lipids) lists 54 different variants of phosphatidylcholine (lecithin) on its website (see listing attached as Exhibit B).

Given the vast number of possible synthetic cardiolipins and synthetic lecithins that could have been combined, there was no *a priori* reason at the time the invention was made to combine tetramyristoyl cardiolipin and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine until Applicants explained the significance of the combination.

Moreover, as explained by Barner (at column 1, lines 33-36), "[cardiolipin] analogues as have been synthesized have demonstrated little or no activity in the serological syphilis test in comparison with cardiolipin . . . ." Therefore, at the time the invention was made, one of skill in the art would have no reasonable expectation of success in a composition comprising a synthetic cardiolipin, such as recited in amended claims 1 and 22-24.

In view of the foregoing arguments and the previously discussed claim amendments, Applicants request that this rejection be withdrawn.

Claims 12, 18, 19, and 25 have been rejected under 35 U.S.C. §103 as allegedly being unpatentable over Yabusaki in view of Avanti Polar Lipids product numbers 710332 (1,1',2,2'-tetramyristoyl cardiolipin) and 850457 (1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine). Applicants traverse this rejection on the grounds that a *prima facie* case of obviousness has not been established.

As an initial matter, claims 18 and 19 have been cancelled; therefore, the rejection is moot with regard to those claims.

Amended claims 12 and 25 each claim methods that recite, in relevant part, "tetramyristoyl cardiolipin and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine." For the same reasons discussed in connection with the rejection of claims 1, 9, 10, and 22-24 under 35 U.S.C. §103 (see above), one of skill in the art would have no reason to combine tetramyristoyl cardiolipin and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine to practice the claimed method. Nor, at the time the invention was made, would the combination of tetramyristoyl cardiolipin and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholinone in the claimed method have

a reasonable expectation of success. Thus, a *prima facie* case of obviousness has not been established, and Applicants request that the rejection be withdrawn.

Amendments to the Specification:

Three paragraphs of the specification have been amended to include the range of 0.01 to 0.05% cardiolipin by volume, which is supported by original claim 16.

Newly Added Claims:

Claim 26 is supported, at least, by original claim 20.

Claim 27 is supported by the specification, at least, at page 11, lines 4-5, and at page 14, lines 27-29.

CONCLUSION

It is respectfully submitted that the present claims are in a condition for allowance. If it may further issuance of these claims, the Examiner is invited to call the undersigned at the telephone number listed below.

Respectfully submitted,

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